UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/535,243 | 12/20/2005 | Ghisalberti Carlo | MARGI-0044 | 5778 |

23599 7590 11/20/2009

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

| EXAMINER | |
|---|---|
| WESTERBERG, NISSA M | |
| ART UNIT | PAPER NUMBER |
| 1618 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/20/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/535,243 | CARLO, GHISALBERTI | |
| | Examiner | Art Unit | |
| | Nissa M. Westerberg | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 - 6, 8 - 20* is/are pending in the application.

4a) Of the above claim(s) *8 - 10, 15, 17, 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 6, 11 - 14, 16, 19, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' arguments, filed July 27, 2009, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

### *Election/Restrictions*

1. Claim 6 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of hydroxypyridonone as claim 6 depends from claim 8.

### *Claim Rejections - 35 USC § 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1 – 6 and 20 were rejected under 35 U.S.C. 102(b) as being anticipated by Bissett et al. (WO 95/27485). Bissett et al. does not teach the topical administration of deferiprone to the patient population recited in the claim. Therefore, in light of the amendments to the claims, this rejection is WITHDRAWN.

## *Claim Rejections - 35 USC § 103*

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1, 2, 11 – 13, 16, 19 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. (WO 95/24785) in view of Perricone (US 2002/0013361). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed February 26, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that Bissett et al. discloses numerous compound for the treatment of free radical damage that are iron chelating compounds that reduce the level of free radical damage in mammalian cells. One compound may be deferiprone and the compounds may be delivered by several methods, including topically. Perricone discloses that lipoic acid is useful to treat

rosacea but doe not teach or suggest that lipoic acid is an iron chelator or a hydroxypyridonone compound of formulae (I-III). A skilled worker would have no motivation to combine Bissett or Perricone in order to use deferiprone, an iron chelator.

These arguments are unpersuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, applicants have not addressed why the teaching of Bissett et al. as to compounds that reduce free radical damage would not be applied to treat a skin condition that is treated by a compound that prevents or reduces free radical damage in skin.

As Applicants have stated, deferiprone is taught by Bissett et al. to reduce the level of free radical damage in mammalian cells. Perricone discloses that rosacea is a skin condition that is treated by lipoic acid, an antioxidant that appears to prevent free radical damage to cells and cellular components (see p 5 of February 26,2 009 Office Action and ¶ [0015] of Perricone). Applicants have not addressed why it would not be obvious to one of ordinary skill in the art to treat rosacea using a different compound known in the art to reduce free radical damage as lipoic acid is known in the art to reduce free radical damage and to treat rosacea and telangiectasia. Perricone may not

state that lipoic acid is a metal chelator, but the reasoning for the effectiveness of lipoic acid and deferiprone to treat SMD is not based on the premise that the rosacea or telangiectasia treating agent are iron chelators but rather that the active agent reduces free radical damage, a function which both lipoic acid and deferiprone are taught in the cited prior art to possess.

6. Claims 1, 2, 11 – 14, 16, 19 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. and Perricone further in view of the purpura entry from DermNet NZ. This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed February, 26, 2009 and those set forth below.

In addition to the arguments presented above in regards to Bissett et al. and Perricone, Applicant argues that the DermNet NZ references relate to etiopathological causes of select skin microcirculatory disorders. There is no indication that any of these pathologies are generated by free radical damage or a problem arising from the presence of excess iron. Accordingly, a skilled worker having knowledge of the etiopathology discussed above would not try to treat said diseases with a compound of formula I-III. The suggested treatment of this purpura suggested by the reference is identification and treatment of the underlying causes of purpura. Nowhere is there any suggestion that the application of an iron chelator (e.g., deferiprone) would be successful in the treatment of SMD's and deferiprone does not interfere in any of etiopathological causes thereof.

These arguments are unpersuasive. Perricone teaches that the topical application of an agent that reduces or prevents free radical damage to treat skin damage, particularly inflammation and aging, including rosacea, a condition which is characterized by chronic inflammation of the blood vessels with papule and pustules superimposed over erythema and telangiectasia (visible blood vessels; p 5 of February 26, 2009 Office Action and ¶¶ [0004] and [0015] of Perricone). The symptoms described for rosacea of inflammation and diffuse erythema (abnormal redness of the skin) overlap with the purpura symptoms of erythematous inflammation.

While the DermNet NZ entry indicates that identification and treatment of the underlying cause, identification and treatment of the underlying cause of a condition is not always possible. Even if that cause can be identified and treated, treatment of the symptoms in conjunction with treatment of the underlying cause may result in faster relief of the visible symptoms than treatment of the underlying condition alone. The instant claims do not require treatment of the underlying cause of the SMD but rather treating the SMD. As agents that reduce free radical damage in the skin are shown by the cited prior art to treat symptoms that are exhibited in both rosacea and purpura, one of ordinary skill in the art would be motivated to treat those same symptoms in the skin despite the fact that the inflammation and skin redness may present with slightly different symptoms.

7. Claims 1 – 3, 11 – 13, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. and Perricone as applied to claims 1, 2, 11 – 13,

16, 19 and 20 above, and further in view of the DermNet NZ entry for cutaneous vasculitis (a copy provided with the March 4, 2008 Office Action).

Bissett et al. discloses an emulsion composition comprising 1,2-dimethyl-3-hydroxy-pyrid-4-one (deferiprone) that is applied to twice daily to the skin (p 16, ln 8 – 29). Pharmaceutically acceptable salts of the active ingredient can also be used (p 2, ln 3 – 8). The active ingredient are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, ln 8 – 10). It is believed that the compounds bind to iron in such a way so that the iron cannot participate in the formation of radical species (p 2, ln 14 – 18). Perricone discloses that patients with rosacea, a chronic inflammation disorder affecting the blood vessels of the face, suffer from papule and pustules superimposed on diffuse erythema and telangiectasia (visible blood vessels) over the central portion of the face (¶ [0004]). The treatment of rosacea is the topical application of a composition comprising lipoic acid (¶ [0019]). Lipoic acid has been suggested for the treatment of inflammation and aging of the skin as because of its antioxidant activity, as it appears to prevent free radical damage (¶ [0015]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to topically apply deferiprone to a patient suffering from rosacea and/or telangiectasia. One of ordinary skill would have been motivated and reasonably would have expected success as Bissett et al. teaches that topical application of deferiprone decreases free radicals by way of iron chelation in the skin and Perricone teaches that rosacea and telangiectasia can be treated by topical application of an agent which decreases free radicals in the skin.

Neither reference discloses the treatment of patients with cutaneous vasculitis.

Cutaneous vasculitis is a condition in which the blood vessels of the skin become inflamed (p 1, ¶ 1). The disease presents with various red spots, usually on the limbs (p 3). In many cases the underlying cause is not found (p 1, ¶ 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat the inflammation associated with cutaneous vasculitis by administration of deferiprone. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Bissett et al. discloses that deferiprone reduces free radical activity in mammalian tissues and Perricone discloses that the topical administration of agents that reduce free radicals also reduces the inflammation associated with skin conditions like rosacea. By treating the inflammation response that leads to vasculitis, at least the symptoms of inflammation, if not the underlying cause of the inflammation itself, will be treated, resulting in the treatment of the cutaneous vasculitis.

8. Claims 1, 2, 5, 11 – 13, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bissett et al. and Perricone as applied to claims 1, 2, 11 – 13, 16, 19 and 20 above, and further in view of the DermNet NZ entry for capillaritis (a copy provided with the March 4, 2008 Office Action).

Bissett et al. discloses an emulsion composition comprising 1,2-dimethyl-3-hydroxy-pyrid-4-one (deferiprone) that is applied to twice daily to the skin (p 16, ln 8 – 29). Pharmaceutically acceptable salts of the active ingredient can also be used (p 2, ln

3 – 8). The active ingredient are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, ln 8 – 10). It is believed that the compounds bind to iron in such a way so that the iron cannot participate in the formation of radical species (p 2, ln 14 – 18). Perricone discloses that patients with rosacea, a chronic inflammation disorder affecting the blood vessels of the face, suffer from papule and pustules superimposed on diffuse erythema and telangiectasia (visible blood vessels) over the central portion of the face (¶ [0004]). The treatment of rosacea is the topical application of a composition comprising lipoic acid (¶ [0019]). Lipoic acid has been suggested for the treatment of inflammation and aging of the skin as because of its antioxidant activity, as it appears to prevent free radical damage (¶ [0015]).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to topically apply deferiprone to a patient suffering from rosacea and/or telangiectasia. One of ordinary skill would have been motivated and reasonably would have expected success as Bissett et al. teaches that topical application of deferiprone decreases free radicals by way of iron chelation in the skin and Perricone teaches that rosacea and telangiectasia can be treated by topical application of an agent which decreases free radicals.

Neither reference discloses the treatment of patients with skin capillaritis.

Capillaritis is also known as pigmented purpura in which reddish brown patches appear on the skin which are caused by inflamed, leaky capillaries (p 1, ¶¶ 1 - 2). Various types including itching purpura and purpura annularis telangiectodes,

depending on the particular set of symptoms associated with the spots in a particular patient (section bridging p 1 – 2).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to treat the inflammation associated with cutaneous vasculitis by administration of deferiprone. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Bissett et al. discloses that deferiprone reduces free radical activity in mammalian tissues and Perricone discloses that the topical administration of agents that reduce free radicals also reduces the inflammation associated with skin conditions like rosacea. By treating the inflammation response that leads to the leaking of the capillaries which presents as reddish brown patches, at least the symptoms of inflammation, if not the underlying cause of the inflammation itself, will be treated, resulting in the treatment of capillaritis in one of its form such as itching purpura or purpura annularis telangiectodes.

9. Claims 1 – 5, 11 – 14, 16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghisalberti et al. (WO 01/17497) in view of Murad (US 6,630,163). This rejection is MAINTAINED for the reasons of record set forth in the Office Actions mailed march 4, 2008, September 5, 2008 and February 26, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that Ghisalberti '497 is directed towards the treatment of pathologies resulting from impaired melanocyte activity which

may comprise 3-hydroxypyr(id)one derivatives. As noted above in the DermNet NZ reference, the claimed pathologies are not in any way related to the production of melanin resulting in hyperpigmentation. The spots described by this reference are the result of blood fluid leakage at an injection site and not the result of a pathology caused by a SMD. Hemoglobin in injection site blood leakage is promptly bound to dermal and connective protein to form hemosiderin deposits, which in turn may stimulate the activity of surrounding melanocytes. A skilled worker would recognize that hemosideric spots do not arise from SMD. Ghisalberti is silent regarding the treatment of SMD's. Murad teaches the use of fruit extracts for neutralizing free radicals and is silent regarding iron chelators. The reference broadly teaches a method for treating almost any dermatological disorder, including some MSDs. Whatever its merits, Murad does not teach that an agent useful for treating hyperpigmented skin is useful for treating MSD and vice versa. Fruit extracts are not known to be iron chelators. The fruit extracts can be used to treat any dermatological condition due to the anti-free radical properties so a variety of pathologies or very different etiologies can be "treated". The '163 patent makes incredible claims but a skilled worker would recognize that one agent cannot credibly be used to treat all the pathologies listed.

These arguments are unpersuasive. Certain types of hyperpigmentation and the SMD purpura are associated with the presence of components of the blood outside the blood vessels. Applicants have not presented any evidence as to the difference in the events that occur following leakage of hemoglobin from an injection site versus the

leakage from the blood vessels that occur in the various SMDs. Arguments without factual support are mere allegations and are not found to be persuasive.

The Murad patent claims the management of one or more dermatological conditions by topically administering a composition that comprises a pomegranate extract, moisturizing agents and a hydroxy acid in a carrier and the specification indicates that these conditions include a variety of conditions including hyperpigmentation, and senile purpura (col 16, ln 46 – 57). Free radical damage and inflammation, for example, are associated with a wide variety of conditions so agents that reduce or prevent such damage have the potential to be efficacious in treating a wide variety of conditions. Applicants arguments are sufficient to overcome the presumption of validity associated with an associated an issued U.S. patent.

In the absence of evidence to support the allegations of Applicant in regards to the mechanism of hemoglobin following leakage from the blood vessel and the lack of credibility associated with the claims of the Murad patent, these arguments are not found persuasive so this rejection is maintained.

## ***Conclusion***

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jake M. Vu/
Primary Examiner, Art Unit 1618

NMW